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Titanocene(II)-promoted carbonyl cyclopropylidenation utilizing 1,1-dichlorocyclopropanes

Tomohiro Shono, Takehiro Nagasawa, Akira Tsubouchi and Takeshi Takeda*

Department of Applied Chemistry, Graduate School of Engineering, Tokyo University of Agriculture and Technology, Koganei, Tokyo 184-8588, Japan

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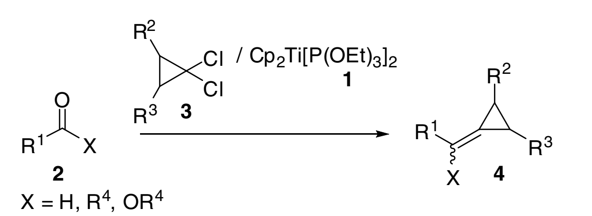
Abstract—A variety of alkylidenecyclopropanes bearing various substituents on their cyclopropane ring were obtained by the titanocene(II)-promoted reaction of 1,1-dichlorocyclopropane derivatives with carbonyl compounds including esters and lactones.

Because of their unique reactivity, highly strained alkylidenecyclopropanes are useful intermediates in organic synthesis.[1] These compounds are employed, for example, for [3+2] cycloaddition,[2] [4+2] cycloaddition,[3] [2+2] cycloaddition,[4] and preparation of cyclobutenes.[5] Therefore, a number of methods have been developed for their preparation.[3b,6] Among them, cyclopropylidenation of carbonyl compounds is the most straightforward and the Wittig,[7] Horner–Wadsworth–Emmons,[8] Peterson,[2a,9] and Julia-Kocienski[5a] reactions have been used for the transformation of aldehydes and ketones to alkylidenecyclopropanes. The Julia-Lythgoe olefination, which requires multi-step conversion, has also been employed for this purpose.[10] These reactions, however, suffer two major drawbacks: there is considerable difficulty in the introduction of substituents on the cyclopropane ring and they cannot be applied to the cyclopropylidenation of carboxylic acid derivatives. Although Petasis and Bzowej have overcome the latter difficulty by the use of cyclopropylidenetitanocene generated by the α-elimination of dicyclopropyltitanocene,[11] the procedure requires the preparation of cyclopropyllithiums, and hence the preparation of alkylidenecyclopropanes bearing substituents on the cyclopropane ring seems to be troublesome.

We have developed a new procedure for the Wittig-type olefination of carbonyl compounds using *gem*-dichlorides and the titanocene(II) reagent $Cp_2Ti[P(OEt)_3]_2$ **1**. Alkylidenation,[12] dichloromethylidenation,[13] and vinylidenation[14] are successfully achieved by the low-valent titanium reagent **1**-promoted reactions of carbonyl compounds with the corresponding *gem*-dichlorides. Here we describe the cyclopropylidenation of carbonyl compounds **2** utilizing a dichlorocyclopropane **3**-titanocene(II) **1** system, which provides a convenient tool for the preparation of alkylidenecyclopropanes **4** (Scheme 1). The procedure enjoys advantages over the above conventional methods that a variety of starting materials, dichlorocyclopropanes **3**, are readily available by the dichlorocyclopropanation of olefins with $CHCl_3$–NaOH[15] and it can be applied to the cyclopropylidenation of esters and lactones as well as aldehydes and ketones.

When 7,7-dichlorobicyclo[4.1.0]heptane (**3a**) (2 equiv) was successively treated with the titanocene(II) reagent **1** (5 equiv) and 1,5-diphenylpentan-3-one (**2a**), alkylidenecyclopropane **4a** was obtained in 64% yield (Table 1, entry 1). Similarly titanocene(II) **1**-promoted reaction of 1,1-dichlorocyclopropanes **3** bearing different substit-



Scheme 1.

Keywords: Cyclopropanes; Carbonyl compounds; Olefination; Titanocene(II).

* Corresponding author. Tel./fax: +81 42 388 7034; e-mail: takeda-t@cc.tuat.ac.jp

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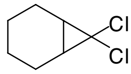
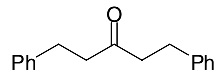
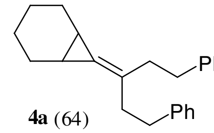
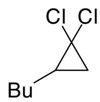
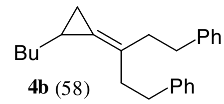
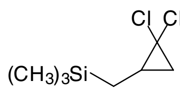
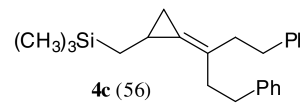
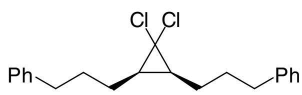
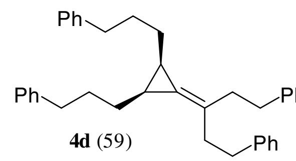
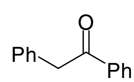
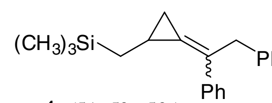
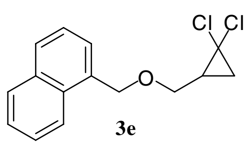
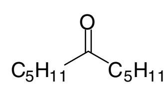
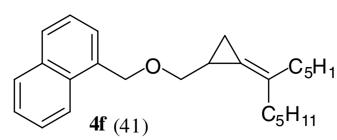
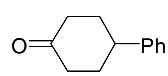
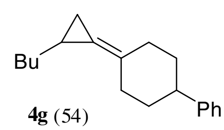
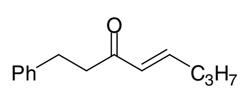
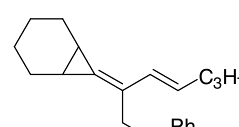
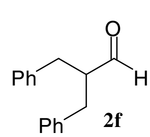
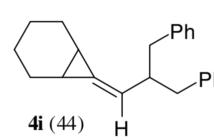
Table 1. Preparation of alkylidenecyclopropanes **4**[a]

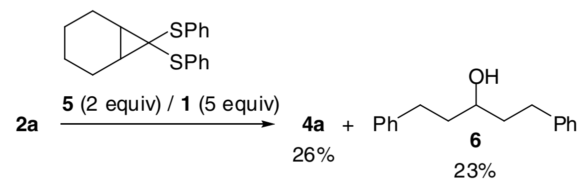
Entry	Dichloride **3**	Carbonyl compound **2**	Alkylidenecyclopropane **4** (yield/%)[b]
1	 **3a**	 **2a**	 **4a** (64)
2	 **3b**	**2a**	 **4b** (58)
3	 **3c**	**2a**	 **4c** (56)
4	 **3d**	**2a**	 **4d** (59)
5	**3c**	 **2b**	 **4e** (51; 50 : 50[c])
6	 **3e**	 **2c**	 **4f** (41)
7	**3b**	 **2d**	 **4g** (54)
8	**3a**	 **2e**	 **4h** (58)
9	**3a**	 **2f**	 **4i** (44)

[a] All the reactions were performed with a similar procedure as described in the text.
[b] Isolated yields based on carbonyl compounds used.
[c] Ratio of stereoisomers.

uents with ketones gave alkylidenecyclopropanes **4** (entries 2–7). Synthetic advantage of this method was demonstrated by the use of heteroatom-substituted dichlorocyclopropanes **3c** and **3e**, which were easily prepared from the corresponding allylsilane and allyl ether and subjected to the cyclopropylidenation to produce the olefination products **4c**, **4e**, and **4f** (entries 3, 5, and 6). Diene **4h** was successfully prepared by the reaction of α,β-unsaturated ketone **2e** (entry 8). Aldehyde **2f** could be employed as a carbonyl component though the yield of alkylidenecyclopropane **4i** was moderate (entry 9).

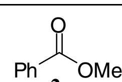
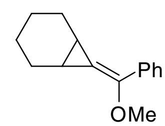
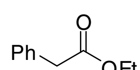
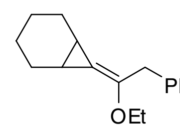
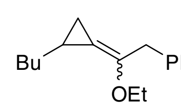
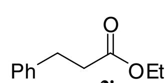
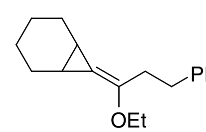
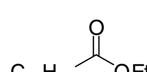
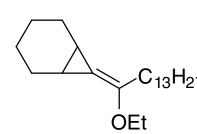
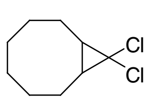
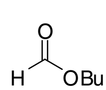
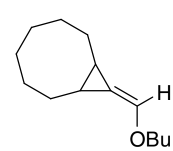
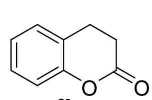
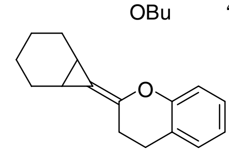
The typical procedure for the alkylidenation of ketones is as follows: finely powdered molecular sieves 4 Å (250 mg), magnesium turnings (61 mg, 2.5 mmol), and Cp_2TiCl_2 (623 mg, 2.5 mmol) were placed in a flask and dried by heating with a heat gun under reduced pressure (2–3 mm Hg). After cooling, THF (5 mL) and triethyl phosphite (0.86 mL, 5.0 mmol) were added successively with stirring at 25 °C under argon, and the reaction mixture was stirred for 3 h. A THF (0.8 mL) solution of **3a** (165 mg, 1.0 mmol) was added to the mixture at −10 °C and stirring was continued for 1 h at the same temperature. A THF (0.8 mL) solution of **2a** (119 mg, 0.5 mmol) was added to the mixture which was then refluxed for 2 h. After cooling to room temperature, the reaction was quenched by addition of 1 M NaOH (30 mL). The insoluble materials were filtered off through Celite and washed with ether (40 mL). The layers were separated, and the aqueous layer was extracted with ether (2 × 20 mL). The combined organic extracts were dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by PTLC (hexane) to give **4a** (102 mg, 64%).

Contrary to the above results, the titanocene(II) **1**-promoted reaction of **2a** with 7,7-bis(phenylthio)bicyclo-[4.1.0]heptane **5** was rather complicated. After the treatment of **5** (2 equiv) with **1** (5 equiv) at 25 °C for 15 min, **2a** was added to the reaction mixture to produce cyclopropylidenation product **4a** only in low yield along with alcohol **6** formed by the reduction of **2a** with **1** (Scheme 2). Substantial amounts of the starting materials **2a** (24%) and **5** (15%) were also recovered. The result is in a sharp contrast with the fact that a titanocene(II) **1**-1,1-bis(phenylthio)cyclobutane system is effective for

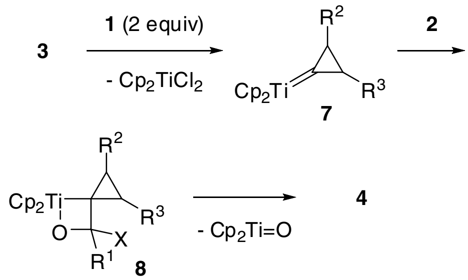


Scheme 2.

Table 2. Preparation of (1-alkoxyalkylidene)cyclopropanes **4**[a]

Entry	Dichloride 3	Carboxylic acid derivative 2	Alkylidenecyclopropane 4 (yield/%)[b]
1	**3a**	 **2g**	 **4j** (60)
2	**3a**	 **2h**	 **4k** (66)
3	**3b**	**2h**	 **4l** (49)[c]
4	**3a**	 **2i**	 **4m** (64)
5	**3a**	 **2j**	 **4n** (46)
6	 **3f**	 **2k**	 **4o** (51)
7	**3a**	 **2l**	 **4p** (55)[d]

[a] All the reactions were carried out with a similar procedure as described in Ref. 17.
[b] Isolated yields based on the carboxylic acid derivatives used.
[c] Mixture of stereoisomers. The ratio was not determined.
[d] Contaminated with triethyl phosphite and triethyl phosphate. The yield was corrected for the contaminants.



Scheme 3.

the cyclobutylidenation of a wide variety of carbonyl compounds.[16]

This olefination is also applicable to carboxylic acid derivatives. Alkylidenecyclopropanes **4** bearing an enol ether substructure were obtained by the reaction of **3** with esters (Table 2, entries 1–5). The reactions of formic ester **2k** and lactone **2l** also gave the corresponding enol ethers **4** (entries 6 and 7). Since these enol ethers are readily hydrolyzed under the work-up and purification conditions described above, the special care should be taken to isolate them in pure forms.[17]

As in the cases of the olefination using *gem*-dichlorides previously reported, the olefination with 1,1-dichlorocyclopropanes **3** is assumed to proceed via the formation of titanium cyclopropylidene complexes **7** generated by the reductive titanation of **3** with **1** (Scheme 3). The subsequent reaction of carbene complexes **7** with carbonyl compounds **2** affords oxatitanacyclobutanes **8**, which give alkylidenecyclopropanes **4** through the expulsion of titanocene oxide.

In conclusion, we have developed the first practical procedure for the preparation of alkylidenecyclopropanes bearing various substituents on their cyclopropane ring utilizing readily available 1,1-dichlorocyclopropanes and titanocene(II) reagent **1**. This procedure is applicable to the cyclopropylidenation of highly enolizable ketones and carboxylic acid derivatives.

Acknowledgments

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17. The typical procedure for the cyclopropylidenation of carbocylic acid derivatives is as follows: To a THF (3 mL) solution of titanocene(II) reagent **1**, prepared from magnesium turnings (38 mg, 1.6 mmol), Cp_2TiCl_2 (374 mg, 1.5 mmol), and $P(OEt)_3$ (0.5 mL, 2.9 mmol) in the presence of molecular sieves 4 Å (150 mg), was added a THF (1 mL) solution of **3a** (99 mg, 0.6 mmol) at 25 °C. After stirring for 10 min, a THF (1 mL) solution of **2h** (49 mg, 0.3 mmol) was added to the reaction mixture, which was then refluxed for 2 h. After cooling, triethylamine (0.3 mL) was added and the reaction mixture was diluted with hexane (20 mL). The insoluble materials were filtered off through Celite and washed with hexane (10 mL). The combined hexane solutions were dried over K_2CO_3. After removal of the solvent under reduced pressure, the residue was chromatographed over alumina gel (eluted with 0.5% triethylamine in hexane) to give **4k** (48 mg, 66%).